Epilepsy & Behavior 37 (2014) 11–15

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Withdrawal-related adverse events from clinical trials of clobazam in Lennox–Gastaut syndrome

Dwain Tolbert [a,*], Stuart I. Harris [b], Ihor Bekersky [a], Deborah Lee [a], Jouko Isojarvi [a]

[a] Lundbeck LLC, Deerfield, IL, USA
[b] SeaView Research, Inc., Miami, FL, USA

ARTICLE INFO

Article history:
Received 21 March 2014
Revised 12 May 2014
Accepted 18 May 2014
Available online xxxx

Keywords:
Clobazam
Lennox–Gastaut syndrome
Withdrawal
Adverse events
Safety
Antiepileptic drug
Benzodiazepine
Clinical trials

ABSTRACT

To assess withdrawal-related adverse event (AE) rates following abrupt clobazam discontinuation in Phase I trials and gradual clobazam tapering (2–3 weeks) following discontinuation from III trials met the criteria for potential/III trials, we evaluated AE data from four multiple-dosage Phase I trials (duration: 8–34 days). Therapeutic (20 and 40 mg/day) and supratherapeutic clobazam dosages (120 and 160 mg/day) were administered. Adverse events (AEs) were also assessed for patients with Lennox–Gastaut syndrome enrolled in Phase II (OV-1002) and Phase III (OV-1012) studies (duration ≤ 15 weeks) and in the open-label extension (OLE) trial OV-1004 (≤5 years). Potential withdrawal-related AEs were identified by preferred terms, provided that the AEs occurred ≥1 day following and ≤30 days after the last clobazam doses, or were deemed withdrawal symptoms by investigators. Clinical Institute Withdrawal Assessment for Benzodiazepines (CIWA-B) scale was used to evaluate withdrawal intensity in three of the four Phase I trials. A total of 207 participants in Phase I trials received steady-state clobazam dosages of 20–160 mg/day, 182 received clobazam dosages of ≥40 mg/day, and 94 received clobazam dosages of ≥120 mg/day. Abrupt clobazam discontinuation led to 193 withdrawal-related AEs for 68 Phase I participants. Nearly 50% of AEs occurred after discontinuation of clobazam dosages of ≥120 mg/day. Adverse events were mild or moderate and included headache (14% of Phase I participants), insomnia (12.6%), tremor (10.1%), and anxiety (8.7%). The CIWA-B scores varied (range: 0–59). Most scores were <30, indicating possible mild benzodiazepine withdrawal. III trials met the criteria for potential/III patients received clobazam dosages of ≤40 mg/day, and those in the OLE trial received clobazam dosages of ≤80 mg/day. Eighty-seven patients discontinued clobazam and were gradually tapered. No withdrawal-related AEs or incidences of status epilepticus were reported. Withdrawal-related AEs observed in Phase I studies following abrupt clobazam discontinuation at therapeutic and supratherapeutic dosages were generally mild. No withdrawal-related AEs occurred when dosages were tapered over 3 weeks, after short- or long-term clobazam use (≤5 years).

1. Introduction

Lennox–Gastaut syndrome (LGS), a severe childhood epileptic encephalopathy, is characterized by slow spike-and-wave electroencephalograms, as well as by occurrence of several seizure types including tonic, atonic, and atypical absence [1]. Most patients with LGS have chronic, treatment-refractory epilepsy throughout childhood and adolescence. Abnormal mental development and behavioral disturbances are common in these patients, and most experience continued neurocognitive impairment that persists into adulthood.

The 1,5-benzodiazepine clobazam (Onfi®) was approved in 2011 by the US Food and Drug Administration as adjunctive treatment for seizures associated with LGS for patients 2 years of age and older [2]. Efficacy and safety of clobazam in patients with LGS have been established in III trials met the criteria for potential/III trials [3–6]. Outside the United States, clobazam has been used to treat anxiety disorders and epilepsy for several decades [2].

The abrupt discontinuation of benzodiazepines often results in a spectrum of adverse events (AEs) related to withdrawal [7–9]. These symptoms often include anxiety, insomnia, irritability, sedation, seizures, and somnolence. To determine the potential withdrawal-

* Corresponding author at: Lundbeck LLC, 4 Parkway North, Deerfield, IL 60015, USA. Tel.: +1 800 455 1141; fax: +1 847 282 1001.
E-mail address: dtol@lundbeck.com (D. Tolbert).

http://dx.doi.org/10.1016/j.yebeh.2014.05.016

related adverse events (AEs) of clobazam, we evaluated data from Phase I trials (during which clobazam dosages were abruptly discontinued) and III trials met the criteria for potential/III epilepsy trials (during which clobazam dosages were tapered gradually).

2. Methods

Potential withdrawal-related AEs following abrupt clobazam discontinuation in four Phase I trials or gradual tapering in three III trials met the criteria for potential/III clobazam trials were assessed. The trials are summarized below.

2.1. Phase I trials (abrupt clobazam discontinuation)

2.1.1. OV-1022

This thorough cardiac conduction (T-QT) study was double-blind, double-dummy, randomized, single-site, 4-arm, and parallel-group in design. The objective of this trial was to examine the potential of clobazam and its primary active metabolite, *N*-desmethylclobazam (*N*-CLB), to have clinically significant effects on cardiac intervals at both therapeutic (40 mg/day) and supratherapeutic (160 mg/day) dosages compared with moxifloxacin (400 mg/day, active control) and placebo. The QT interval is the time between the start of the Q-wave and the end of the T-wave on an EKG.

A total of 280 healthy male and female volunteers were enrolled and divided among the four groups. Treatments were administered under fasting conditions from Days 1 through 29 and discontinued abruptly (no tapering of dosage).

2.1.2. OV-1023

This open-label, multiple-dosage, drug-interaction study assessed the safety, tolerability, and single-dose pharmacokinetics (PK) profiles of a drug cocktail containing midazolam (4 mg), caffeine (200 mg), tolbutamide (500 mg), and dextromethorphan (30 mg), following multiple clobazam dosages. The drug cocktail represents agents that are substrates of certain cytochrome P450 isoenzymes.

A total of 18 healthy male volunteers were enrolled and administered the drug cocktail on the morning of Day 1. Oral clobazam (40 mg) was then administered once daily on Days 4–18, and then a single oral dose of clobazam (40 mg) was coadministered with a single oral dose of the drug cocktail on Day 19 before treatment was discontinued.

2.1.3. OV-1032

The objective of this Phase 1, open-label, multiple-dosage study was to examine the effects of impaired renal function (mild and moderate) on the PK profile of clobazam. Seven participants with mild and six participants with moderate renal impairment (based on estimated creatinine clearance [CL_{CR}] > 50–80 mL/min and CL_{CR} 30–50 mL/min, respectively) and 12 control participants with normal renal function (CL_{CR} > 80 mL/min) were enrolled. Healthy participants were matched to those with renal impairment at the same centers on the basis of age, race, sex, weight, and smoking status. All participants received a single 20-mg dose of clobazam on Day 1 and once-daily clobazam on Days 5–11. Participants fasted overnight prior to study drug administration each morning.

2.1.4. OV-1038

This open-label, single-center, multiple-ascending–dosage study was designed to evaluate the safety, tolerability, and the steady-state PK profile of clobazam in healthy adult participants. Twenty-four participants (male or female) were enrolled and assigned to one of two treatment groups. Data from Group 1 were used to establish the maximum-tolerated-titrated dosage, defined as the greatest dosage in excess of 60-mg/day tolerated-titrated dosage that was tolerated for 3 consecutive days by at least 70% of the individuals who had previously tolerated 60-mg/day tolerated-titrated dosage.

Study medication was administered twice daily under fasting conditions. In Group 1, clobazam was titrated from 10-mg/day tolerated-titrated dosage to 160-mg/day tolerated-titrated dosage, with each dosage administered for at least 3 days prior to dosage increase. The tolerated-titrated dosage was increased by 10- mg/day through 60-mg/day tolerated-titrated dosage and then by 20 mg/day until either 160-mg/day tolerated-titrated dosage was reached or the dosage was deemed intolerable (which included, but was not limited to, assessment by scales and AE monitoring) by investigators. Clobazam administration was concluded with a single morning dose of the maximum tolerated-titrated dosage (80 mg).

In Group 2, dosage titration was performed in a manner similar to Group 1, with the greatest scheduled dosage of 140-mg/day tolerated-titrated dosage. However, based on preliminary safety and PK assumptions, the greatest dosage administered in Group 2 was 120-mg/day tolerated-titrated dosage. Once participants had been titrated to 120-mg/day tolerated-titrated dosage and demonstrated tolerability for 3 days, they then received 120-mg/day tolerated-titrated dosage for an additional 11 days, followed by a final morning dose of 60 mg.

2.2. III trials met the criteria for potential/III trials (gradual clobazam tapering)

In trials OV-1002, OV-1012, and OV-1004, patients who discontinued were gradually tapered off clobazam.

2.2.1. OV-1002 and OV-1012

Trial OV-1002 was a Phase II, multicenter, randomized, double-blind, dosage-ranging, parallel-group study designed to assess the efficacy and safety of clobazam as adjunctive therapy to a stable regimen of antiepileptic drugs (AEDs) in patients 2–30 years of age with LGS [3]. The study consisted of a 4-week baseline period, a 3-week titration period, a 4-week maintenance period, and a 3-week taper period, with a final visit 1 week after last dose for patients not continuing in the open-label extension (OLE) study OV-1004.

The Phase III OV-1012 trial (also known as CONTAIN[4]) was a multicenter, randomized, double-blind, placebo-controlled study that assessed the efficacy and safety of clobazam as adjunctive therapy to a stable AED regimen in patients 2–60 years of age with LGS [4]. The study included a 4-week baseline period, a 3-week titration period, and a 12-week maintenance period, followed by either continuation in the OV-1004 OLE or a 2- to 3-week taper period (depending on patients' weights), with a follow-up visit 1 week after the last clobazam dose.

In trial OV-1002, patients were randomly assigned to low-dosage clobazam (0.25 mg/kg up to a maximum daily dosage of 10 mg/day) or high-dosage clobazam (1.0 mg/kg, up to a maximum daily dosage of 40 mg/day). In trial OV-1012, patients were randomly assigned to placebo, low-dosage clobazam (0.25 mg/kg/day, maximum daily dosage of 10 mg/day), medium-dosage clobazam (0.5 mg/kg/day, maximum daily dosage of 20 mg/day), or high-dosage clobazam (1.0 mg/kg/day, maximum daily dosage of 40 mg/day). For both trials, study medication was administered twice daily. During titration, clobazam was initiated at either 5 mg/day or 10 mg/day. Dosages were then increased every 7 days until assigned target dosages were attained. Clobazam was administered twice daily. Investigators could decrease daily clobazam dosages by a single tablet (placebo or clobazam dosage of 5 mg/day) if a patient developed signs or symptoms of drug intolerance. The minimum clobazam dosage was 5 mg/day.

2.2.2. OV-1004

Patients from trials OV-1002 and OV-1012 were given the option of enrolling in OV-1004, a multicenter, OLE study of clobazam as adjunctive therapy in patients with LGS [5,6]. The objective of this OLE trial was to collect safety and efficacy information regarding long-term clobazam usage in patients with LGS.